IGA FC-FOLATE CONJUGATES, PHARMACEUTICAL COMPOSITIONS AND METHODS TO TREAT CANCER

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of co-pending U.S. patent application Ser. No. 15/227,747, filed Aug. 3, 2016, which in turn claims priority to U.S. Provisional Patent Application No. 62/200,463 filed on Aug. 3, 2015. These earlier filed applications are incorporated herein by reference in their entirety as if fully set forth herein.

FIELD OF THE DISCLOSURE

[0002] The present disclosure provides IgA antibody fragment crystallizable region (Fc)-Folate conjugates that selectively target and kill cancer cells expressing folate receptors. The Fc-Folate conjugates are particularly useful to treat breast cancer, including triple negative breast cancer, as well as ovarian and lung cancers.

BACKGROUND OF THE DISCLOSURE

[0003] According to the American Cancer Society, approximately 1 in 8 women in the U.S. will develop breast cancer at some point in their life (1). Of these women, 15-20% will be diagnosed with triple negative breast cancer (TNBC), an aggressive subtype of breast cancer with a high mortality rate (2). TNBC refers to breast tumors that lack the receptors for estrogen (ER), progesterone (PR), and epithelial growth factor (HER2) and therefore, are not dependent on them for growth. Because of this, these tumors do not respond to current hormonal therapy or therapy that targets the HER2 receptor. Of these women who are diagnosed with TNBC, approximately 23% will not survive five years (3). Of the women who survive beyond the first five years, another 20% will suffer a recurrence within 10 years of their treatment. Thus, although TNBC accounts for only 15-20% of new breast cancer patients, it is responsible for 66% of all breast cancer-related deaths (2).

SUMMARY OF THE DISCLOSURE

[0004] The high mortality rate of triple negative breast cancer (TNBC) is due to the fact that there is no effective targeted therapeutic treatment for TNBC. The only current treatment options involve the use of chemotherapeutic drugs that cause various toxicities by simply targeting highly replicating cells such as those of the immune system, the gastrointestinal epithelia and hair follicles. Thus, being able to directly target TNBC tumors would be beneficial in reducing mortality as well as reducing drug toxicity associated with these chemotherapeutic agents.

[0005] The present disclosure provides targeted therapies for TNBC in the form of IgA antibody Fc-folate conjugates.

BRIEF DESCRIPTION OF THE FIGURES

[0006] FIG. **1**. An Fc-folate conjugate triggers neutrophil (PMN)-mediated cancer cell apoptosis by antibody-dependent cellular-cytotoxicity (ADCC). Binding of the folate component of the conjugate to its folate receptor (FRA) present on cancer cells allows binding of the Fc fragment to its receptor (FcαR1) on the PMN. This binding cross-links FcαR1 receptors, triggering ADCC through the release of cytotoxic enzymes resulting in cancer cell apoptosis.

[0007] FIG. **2**. FRA expression in triple negative breast cancer (TNBC) cells in the presence of high and low folate levels. Cells were grown for at least one week in either RPMI-1640 containing supra-physiological levels of folate (2.3 mM) or in folate-free RPMI and in the presence of 10% serum containing approximately 0.02 mM folate. FRA message was measured using RT-QPCR and human ovarian cancer cells (HeLa) were used as a positive control. Results are mean+/−SEM where * $P<0.05$ compared to low folate treated cells.

[0008] FIG. **3**. Binding of folate to TNBC cells. Cells were incubated on ice for 1 hour with ^{3}H-labeled folate (0.0318 mM, 14.3 Ci/mmol) in the presence or absence of cold folate (1 mM). ^{3}H-folate binding was significantly inhibited in the presence of cold folate in all cell lines tested. Error shown is +/−SEM where * is $P<0.05$ compared to ^{3}H-folate wells with no cold folate added.

[0009] FIG. **4**. PMN-mediated ADCC of TNBC cells in the presence of a folate-IgA conjugate. MDA-MB-468, or HeLa (control) cells were incubated with PMNs at a ratio of 1:10 (TNBC:PMN) in the presence of folate-IgA (5 μg/ml) or IgA (5 μg/ml) alone for 3 hours. After 3 hours, MTT substrate was added for 45 min. Results represent the absorbance values of the substrate which is indicative of cell viability. Cell viability was significantly reduced after treatment with folate-IgA in both the MDA-MB-468 and HeLa+ PMN co-cultures compared to only IgA containing co-cultures. * $P<0.05$.

DETAILED DESCRIPTION

[0010] According to the American Cancer Society, approximately 1 in 8 women in the U.S. will develop breast cancer at some point in their life (1). Of these women, 15-20% will be diagnosed with triple negative breast cancer (TNBC), an aggressive subtype of breast cancer with a high mortality rate (2). TNBC refers to breast tumors that lack the receptors for estrogen (ER), progesterone (PR), and epithelial growth factor (HER2) and therefore, are not dependent on them for growth. Because of this, these tumors do not respond to current hormonal therapy such as tamoxifen or aromatase inhibitors or therapy that targets the HER2 receptor such as Herceptin (trastuzumab). Of these women who are diagnosed with TNBC, approximately 23% will not survive five years (3). Of the women who survive beyond the first five years, another 20% will suffer a recurrence within 10 years of their treatment. Thus, although TNBC accounts for only 15-20% of new breast cancer patients, it is responsible for 66% of all breast cancer-related deaths (2). This high mortality rate is due to the fact that there is no effective targeted therapeutic treatment for TNBC.

[0011] Folate is a small hydrophilic vitamin B molecule that is required for the synthesis of purines and pyrimidines, building blocks for DNA and RNA (42). Folate receptors constitute a family of proteins that together allow for the accumulation of folate in cells and may play a role in supporting growth in the developing embryo and fetus (43). In normal adult tissue, folate receptor alpha (FRA) shows limited expression with its expression being localized to apical surfaces of epithelial cells lining ducts within the kidneys, lungs, thyroid, breast and parotid glands (4, 5, 44, 45). Therefore, FRA in normal adult tissues is inaccessible